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Synthesis of 1,2,4-Triazole Derivatives and Determination of Protonation Constant

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A microwave irradiation method has been developed for the synhesis of some 1,2,4-triazole derivatives using environmentally benign solvent ethanol in open vessels. Twelve 1,2,4-triazole derivatives were synthesized in good yields. The newly synthesized compounds (**2a-f** and **3a-f**) were titrated potentiometrically with tetrabutylammonium hydroxide in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide (DMF) and the half-neutralization potential values and the corresponding pKa values were determined.

Key Words: Microwave prosess, 4,5-Dihydro-1*H*-1,2,4-triazol-5-ones, pKa, Potentiometric titrations, Protonation constants, Non-aqueous solvents.

INTRODUCTION

Microwave process is often applied to know conventional thermal reactions in order to accelerate the reaction and therefore to reduce the process time[1-3]. Heterocyclic form the cores of many pharmaceutically relevant substances. Therefore, many publications in the area of microwave-assisted organic synthesis deal with the preparation of heterocycles[4-8].

Acidity measurements of organic compounds have a long history dating back to the end of the 19th century, when the first pKa was measured. Since then a vast body of data on acidities in various solvents has been collected[9-12]. The measurements have mostly been limited to polar solvents, however, with water being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents. Several studies, involving the formation and investigation of biological activities of some 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives, have been reported[13-23]. It is known that these derivatives have weak acidic properties. The acidity of a compound in a given medium is influenced by both the electronic effects of the substituents and the solvent effects of the medium. Moreover, it is sometimes extremely difficult to assess how much each effect contributes to the acidity. Small differences in acidity between similar molecules are also extremely difficult to interpret and one care must be consider in deciding which structural effect has the main influence on acidity.

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A number of studies have been reported on the protonation constants of these derivatives in different media[24-27], however, little information on the protonation constants of these derivatives in water and organic solvent-water mixtures has been published so far[28-30]. In addition, 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, antiinflammatory, antioxidant, antitumor and anti-HIV properties[31-36]. On the other hand, it is known that 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one rings have weak acidic properties, so some 1,2,4-triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents and the pKa values of the compounds were determined[37-40].

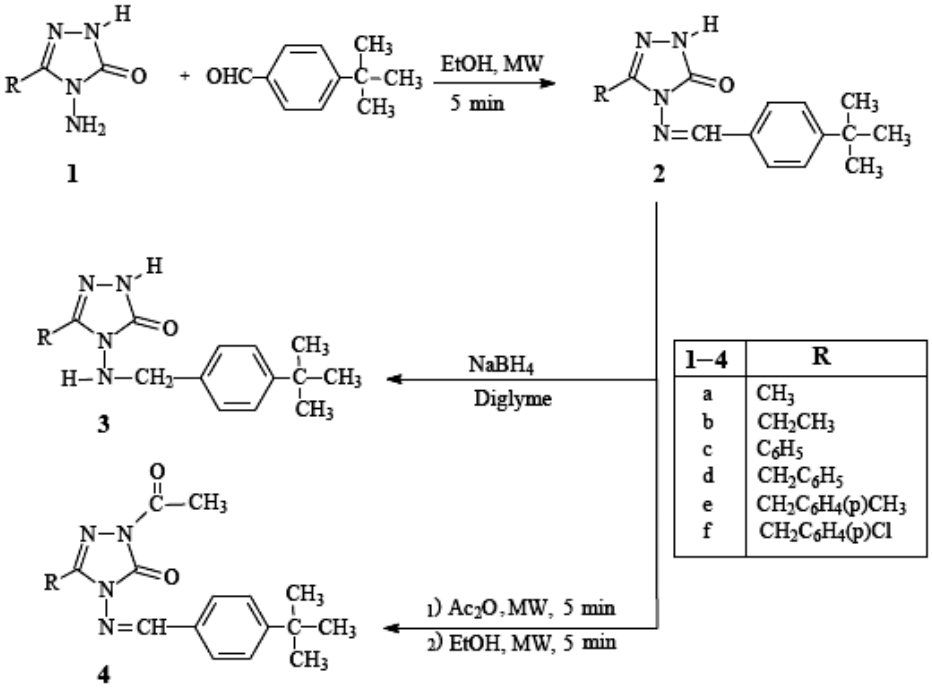
For this purpose, firstly, 3-alkyl-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1a-f**) were synthesized by using the method[41]. Secondly, the reaction of **1a-f** compounds with *t*-butyl benzaldehyde using microwaves led to the formation of 3-alkyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2a-f**). The reduction of imine group in the **2a-f** compounds resulted in the formation of 3-alkyl-4-(*p*-*t*-butyl benzylamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**3a-f**). Finally, 1-acetyl-3-alkyl-4-(*p*-*t*-butylbenzyliden amino)-4,5-dihydro-1,2,4-triazol-5-ones (**4a-f**) were synthesized by the reaction of compounds **2a-f** with acetic anhydride. The typical reaction is shown in **Scheme-I**. Moreover, the potentiometric titrations of the synthesized compounds (**2a-f** and **3a-f**) with tetrabutylammonium hydroxide in non-aqueous solvents such as isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide are examined to determine the corresponding half-neutralization potentials and the corresponding pKa values. The data obtained from the potentiometric titrations was interpreted and the effect of the C-3 substituent in 4,5-dihydro-1*H*-1,2,4-triazol-5-one ring.

EXPERIMENTAL

Synthesis: All chemicals were supplied from Merck and Fluka Co. Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr pellets were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer and ^{1}H NMR in DMSO-d_6 on a Varian 200-A spectrometer using TMS as an internal Standard. The elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General procedure for synthesis of compound 2: Compound **1** (0.01 mol) was dissolved in 10 mL of ethanol and added *p*-*t*-butyl benzaldehyde (0.01 mol). Microwave heating with 350 W for 5 min applied this mixture. The solid (2) which separated out was recrystallized from the appropriate solvent to afford the desired compound **2**.

2a: Yield (91 %), m.p. 190-191 °C. Anal. Calcd. (%) for $C_{14}H_{18}N_4O$; C, 65.12; H, 7.03; N, 21.70. Found (%): C, 65.48; H, 7.01; N, 21.52. IR (KBr, ν_{max}, cm^{-1}): 3194 (NH), 1706 (C=O), 1620 and 1596 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 11.40 (s, 1H, NH), 9.62 (s, 1H, N=CH), 8.00-7.21 (m,4 H, Ar-H), 1.94 (s, 3H, CH_3), 1.28 (s, 9H, *t*-butyl).



Scheme-I

2b: Yield (94 %), m.p. 150-151 °C. Anal. Calcd. (%) for $C_{15}H_{20}N_4O$: C, 66.18; H, 7.41; N, 20.59. Found (%): C, 66.05; H,7.51; N, 20.43. IR (KBr, ν_{max}, cm^{-1}): 3185 (NH), 1701 (C=O), 1605 and 1594 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 11.21 (s, 1H, NH), 10.10 (s, 1H, N=CH), 8.10-7.48 (m, 4H, Ar-H), 2.68 (q, 2H, CH_2), 1.94 (t, 3H, CH_3), 1.14 (s, 9H, *t*-butyl).

2c: Yield (86 %), m.p. 232-233 °C. Anal. Calcd. (%) for $C_{19}H_{20}N_4O$: C, 71.31; H, 6.75; N, 17.50. Found (%): C, 71.04; H, 6.87; N, 17.42. IR (KBr, ν_{max}, cm^{-1}): 3212 (NH), 1706 (C=O), 1604 and 1576 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 11.42 (s, 1H, NH), 9.48 (s, 1H, N=CH), 7.81-7.16 (m, 9H, Ar-H), 1.16 (s, 9H, *t*-butyl).

2d: Yield (92 %), m.p. 206-207 °C. Anal. Calcd. (%) for $C_{20}H_{22}N_4O$: C, 71.92; H, 6.64; N, 16.77. Found (%): C, 71.56; H, 6.70; N, 16.43. IR (KBr, ν_{max}, cm^{-1}): 3176 (NH), 1702 (C=O), 1601 and 1582 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 10.94 (s, 1H, NH), 9.82 (s, 1H, N=CH), 7.48-7.21 (m, 9H, Ar-H), 3.98 (s, 2H, CH_2), 1.12 (s, 9H, *t*-butyl).

2e: Yield (94 %), m.p. 160-161 °C. Anal. Calcd. (%) for $C_{21}H_{24}N_4O$: C, 72.48; H, 6.95; N, 16.10. Found (%): C, 72.24; H, 7.06; N, 15.74. IR (KBr, ν_{max}, cm^{-1}): 3182 (NH), 1704 (C=O), 1603 and 1587 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 10.84 (s, 1H, NH), 9.86 (s, 1H, N=CH), 7.96-7.33 (m, 8H, Ar-H), 3.68 (s, 2H, CH_2), 1.96 (s, 3H, CH_3), 1.48 (s, 9H, *t*-butyl).

2f: Yield (81 %), m.p. 197-198 °C. Anal. Calcd. (%) for $C_{20}H_{21}N_4OCl$: C, 65.91; H, 5.74; N, 15.19. Found (%): C, 65.48; H, 5.88; N, 15.62. IR (KBr, ν_{max}, cm^{-1}): 3178 (NH), 1707 (C=O), 1603 and 1587 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 10.64 (s, 1H, NH), 9.48 (s, 1H, N=CH), 8.11-7.44 (m, 8H, Ar-H), 4.14 (s, 2H, CH_2), 1.14 (s, 9H, *t*-butyl).

General procedure for synthesis of compound 3: To a solution of the corresponding imine **2** (0.01 mol) in warm dry diglyme (30 mL) was added a solution of $NaBH_4$ (0.02 mol) in dry diglyme (20 mL). The mixture was refluxed for 8 h. After cooling, enough amount of water was added to the medium and the mixture allowed to stand overnight at 0-5 °C. The precipitate formed was filtered and washed with cold water. After drying, the product was recrystallized from an appropriate solvent to give compound **3**.

3a: Yield (56 %), m.p. 158-159 °C. Anal. Calcd. (%) for $C_{14}H_{20}N_4O$: C, 64.62; H, 7.75; N, 21.54. Found (%): C, 64.41; H, 7.88; N, 21.56. IR (KBr, ν_{max}, cm^{-1}): 3217 (NH), 3136 (NH), 1699 (C=O), 1590 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 11.24 (s, 1H, NH), 7.60-7.20 (m, 4H, Ar-H), 5.86 (t, 1H, NNH), 4.10 (d, 2H, CH_2), 1.86 (s, 3H, CH_3), 1.44 (s, 9H, *t*-butyl).

3b: Yield (61 %), m.p. 114-115 °C. Anal. Calcd. (%) for $C_{15}H_{22}N_4O$: C, 65.69; H, 8.10; N, 20.44. Found (%): C, 65.42, H, 8.32; N, 20.48. IR (KBr, ν_{max}, cm^{-1}): 3237 (NH), 3156 (NH), 1703 (C=O), 1592 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 10.98 (s, 1H, NH), 7.12 (m, 4H, Ar-H), 5.86 (t, 1H, NNH), 3.92 (d, 2H, CH_2), 2.86 (q, 2H, CH_2), 1.36 (t, 3H, CH_3), 1.22 (s, 9H, *t*-butyl).

3c: Yield (63 %), m.p. 137-138 °C. Anal. Calcd. (%) for $C_{19}H_{22}N_4O$: C, 70.81; H, 6.89; N, 17.39. Found (%): C, 70.62; H, 6.62; N, 17.58. IR (KBr, ν_{max}, cm^{-1}): 3278 (NH), 3166 (NH), 1704 (C=O), 1588 (C=N). ^{1}H NMR (DMSO-d_5): δ ppm, 1.30 (s, 1H, NH), 7.62-6.84 (m, 9H, Ar-H), 6.44 (t, 1H, NNH), 4.00 (d, 2H, CH_2), 1.21 (s, 9H, *t*-butyl).

3d: Yield (58 %), m.p. 151-152 °C. Anal. Calcd. (%) for $C_{20}H_{24}N_4O$: C, 71.43; H, 7.21; N, 16.66. Found (%): C, 71.48; H, 7.36; N, 16.44. IR (KBr, ν_{max}, cm^{-1}): 3288 (NH), 3161 (NH), 1717 (C=O), 1596 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 11.40 (s, 1H, NH), 7.00 (m, 9H, Ar-H), 6.20 (t, 1H, NNH), 3.62 (d, 2H, CH_2), 3.21 (s, 2H, CH_2), 1.12 (s, 9H, *t*-butyl).

3e: Yield (52 %), m.p. 152-153 °C. Anal. calcd. (%) for $C_{21}H_{26}N_4O$: C, 72.01; H, 7.49; N, 16.00. Found (%): C, 72.26; H, 7.23; N, 16.28. IR (KBr, ν_{max}, cm^{-1}): 3312 (NH), 3194 (NH), 1702 (C=O), 1587 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 1.44 (s, 1H, NH), 7.21-6.42 (m, 8H, Ar-H), 6.12 (t, 1H, NNH), 3.98 (d, 2H, CH_2), 3.21 (s, 2H, CH_2), 1.84 (s, 3H, CH_3), 1.23 (s, 9H, *t*-butyl).

3f: Yield (64 %), m.p. 166-167 °C. Anal. Calcd. (%) for $C_{20}H_{23}N_4OCl$: C, 64.70; H, 6.25; N, 15.12. Found (%): C, 64.42; H, 6.40; N, 15.00. IR (KBr, ν_{max}, cm^{-1}): 3296 (NH), 3182 (NH), 1705 (C=O), 1598 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 11.21 (s, 1H, NH), 7.36-6.72 (m, 8H, Ar-H), 5.88 (t, 1H, NNH), 4.11 (d, 2H, CH_2), 3.40 (s, 2H, CH_2), 1.14 (s, 9H, *t*-butyl).

General procedure for synthesis of compound 4: A mixture of **3** (0.01 mol) and acetic anhydride (10 mL) was placed in an Erlenmeyer flask and irradiated by microwave for 5 min. After cooling to room tempereture, 20 mL of absolute ethanol was added and the solution was irradiated by microwave for 5 min. The product was filtered and recrystallized from an appropriate solvent to give compound **4**.

4a: Yield (74 %), m.p. 164-165 °C. Anal. Calcd. (%) for $C_{16}H_{20}N_4O_2$: C, 64.18; H, 6.32; N, 18.26. Found (%): C, 64.01; H, 6.72; N, 18.67. IR (KBr, ν_{max}, cm^{-1}): 1774 (C=O), 1697 (C=O), 1612 and 1596 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 9.81 (s, 1H, N = CH), 8.12-7.36 (m, 4H, Ar-H), 2.68 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 1.16 (s, 9H, *t*-butyl).

4b: Yield (68 %), m.p. 120-121 °C. Anal. Calcd. (%) for $C_{17}H_{22}N_4O_2$: C, 64.97; H, 7.06; N, 17.83. Found (%): C, 64.48; H, 7.19; N, 17.66. IR (KBr, ν_{max}, cm^{-1}): 1773 (C=O), 1696 (C=O), 1618 and 1607 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm 9.98 (s, 1H, N=CH), 8.11-7.58 (m, 4H, Ar-H), 2.78 (s, 3H, CH_3), 2.54 (q, 2H, CH_2), 1.94 (t, 3H, CH_3), 1.04 (s, 9H, *t*-butyl).

4c: Yield (67 %), m.p. 148-149 °C. Anal. Calcd. (%) for $C_{21}H_{22}N_4O_2$: C, 69.62; H, 6.12; N, 15.47. Found (%): C, 69.41; H, 6.28; N, 15.58. IR (KBr, ν_{max}, cm^{-1}): 1761 (C=O), 1702 (C=O), 1601 and 1582 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 9.96 (s, 1H, N=CH), 7.86-6.98 (m, 9H, Ar-H), 2.94 (s, 3H, CH_3), 1.04 (s, 9H, *t*-butyl).

4d: Yield (72 %), m.p. 148-149 °C. Anal. Calcd. (%) for $C_{22}H_{24}N_4O_2$: C, 70.59; H, 6.47; N, 14.97. Found (%): C, 70.42; H, 6.19; N, 15.28. IR (KBr, ν_{max}, cm^{-1}): 1779 (C=O), 1699 (C=O), 1605 and 1590 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 9.78 (s, 1H, N=CH), 7.22-6.48 (m, 9H, Ar-H), 3.46 (s, 2H, CH_2), 2.86 (s, 3H, CH_3), 1.08 (s, 9H, *t*-butyl).

4e: Yield (81 %), m.p. 172-173 °C. Anal. Calcd. (%) for $C_{23}H_{26}N_4O_2$: C, 70.78; H, 6.72; N, 14.36. Found (%): C, 70.46; H, 6.36; N, 14.88. IR (KBr, ν_{max}, cm^{-1}): 1756 (C=O), 1693 (C=O), 1608 and 1587 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 9.84 (s, 1H, N=CH), 7.81-7.12 (m, 8H, Ar-H), 3.54 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.18 (s, 9H, *t*-butyl).

4f: Yield (63 %), m.p. 176-177 °C. Anal. Calcd. (%) for $C_{22}H_{23}N_4O_2Cl$: C, 64.24; H, 5.64; N, 13.63. Found (%): C, 64.02; H, 5.42; N, 13.28. IR (KBr, ν_{max}, cm^{-1}): 1748 (C=O), 1703 (C=O), 1614 and 1589 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm, 10.22 (s, 1H, N=CH), 8.02-7.36 (m, 4H, Ar-H), 3.84 (s, 2H, CH_2), 2.74 (s, 3H, CH_3), 1.04 (s, 9H, *t*-butyl).

Potentiometric titrations: Potentiometric titrations (Fig. 1), an Orion 720A model pH-ionmeter equipped with a combined pH electrode (Ingold) and indicator electrode were used. A magnetic stirrer, a semi-micro burette and a 25 mL beaker were also used in titrations. Before potentiometric titrations, the pH meter was calibrated according to the instructions supplied by the manufactures of the pH meter. During the titrations, the titrant was added in increments of 0.05 mL after each stable reading, and mV values were recorded. The necessary chemicals were

supplied from Fluka and Merck. After purifications, isopropyl alcohol was used to prepare 0.05 N tetrabutylammonium hydroxide. For all potentiometric titrations, 0.05 N tetrabutylammonium hydroxide in isopropyl alcohol, which was prepared from 0.1 N tetrabutylammonium hydroxide (TBAH) by dilution, was used. The 0.05 M solution of TBAH in isopropyl alcohol, which is widely used in the titration of acids, was used as titrant. The mV values, that were obtained in pH-meter, were recorded. Finally, the half-neutralization potential (HNP) values were determined by drawing the mL (TBAH)-mV graphic.

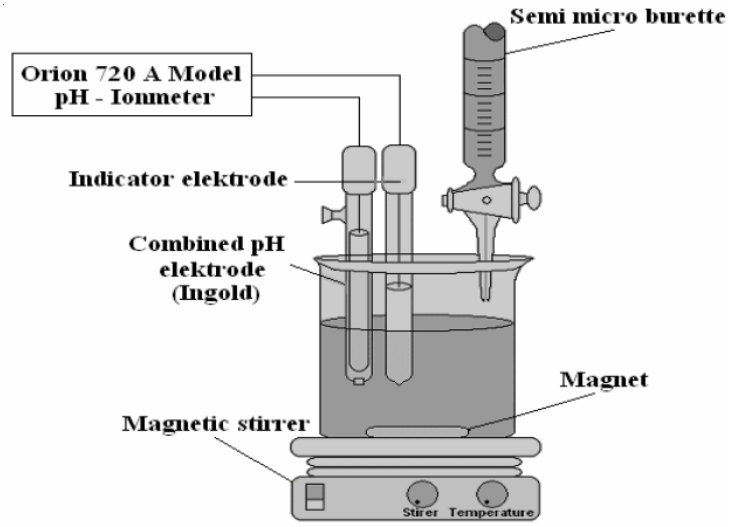


Fig. 1. Potentiometric titration cell

RESULTS AND DISCUSSION

Using classical methods, synthesis of some 3-alkyl(aryl)-4-alkylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were obtained as reported[17-19,22,23]. In this work, similar imine compounds **2** were obtained to reduced reaction times. Furthermore, the acetyl derivatives of 1*H*-1,2,4-triazol-5-ones were reported[42,43]. Similarly, this type acetyl compounds **4** were obtained by using microwave processing to reduced reaction times. In this study, compounds **2a-f** and **3a-f** were titrated potentiometrically with TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide. The mV values read in each titration were drawn against TBAH volumes (mL) added and potentiometric titration curves were formed for all the cases. From the titration curves (Figs. 2-6), the HNP values were measured and the corresponding pKa values were calculated. The half-neutralization potential (HNP) values and the corresponding pKa values of all triazole derivatives, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide, are presented in Table-1.

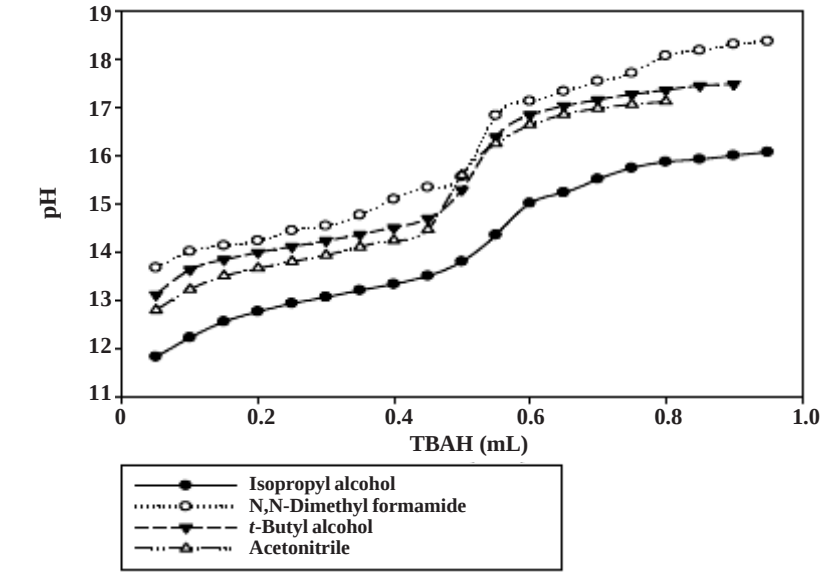


Fig. 2. pH – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **2a** (3-methyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25 °C

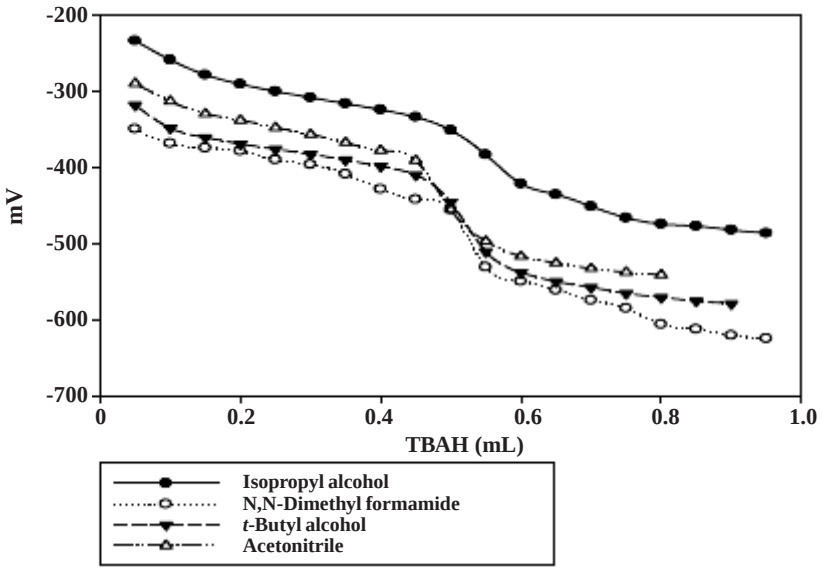


Fig. 3. mV – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **2a** (3-methyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25 °C

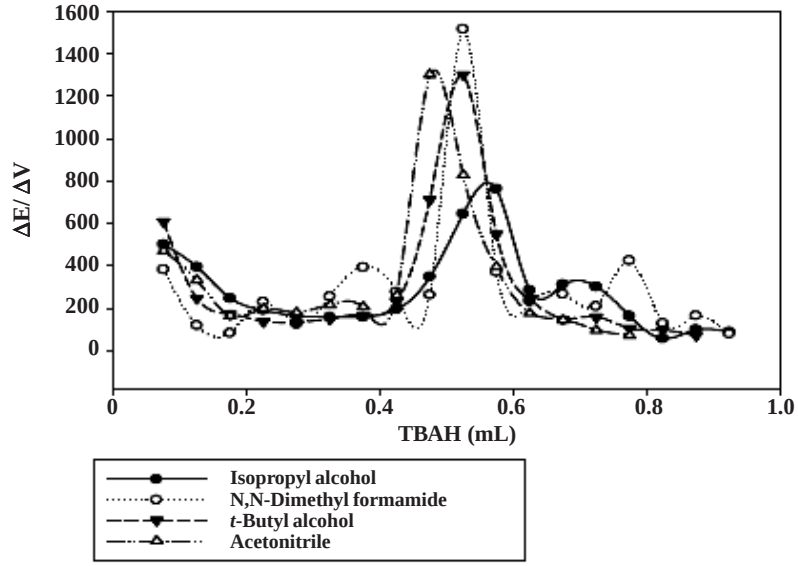


Fig. 4. ΔE/ΔV – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **2a** (3-methyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25 °C

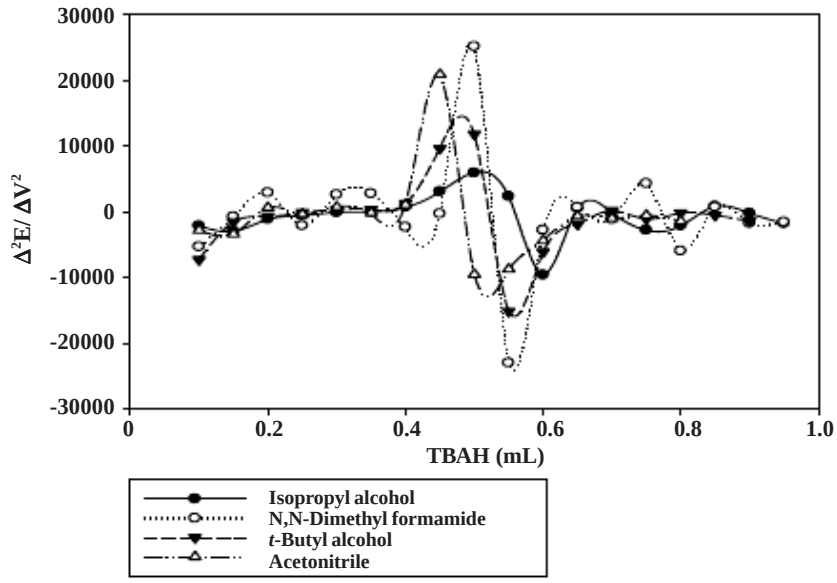


Fig. 5. $\Delta^2E/\Delta V^2$ – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **2a** (3-methyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25 °C

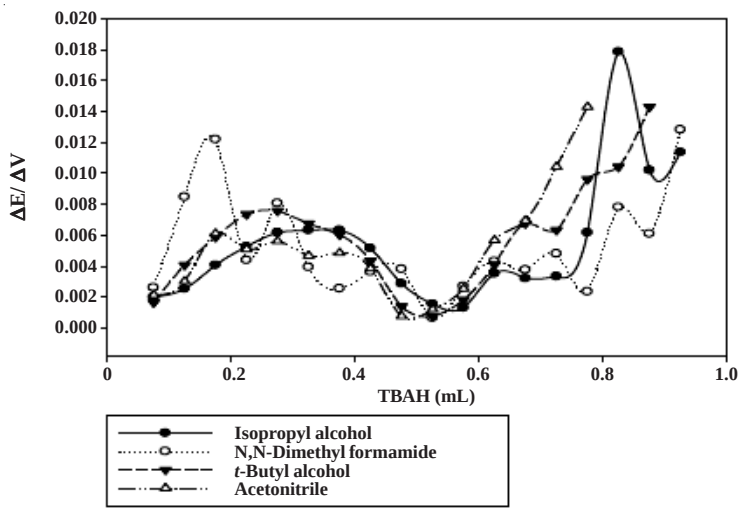


Fig. 6. ΔV/ΔE – mL (TBAH) Potentiometric titration curves of 0.001 M solutions of compound **1** (3-methyl-4-(*p*-*t*-butylbenzylidenamino)-4,5-dihydro-1*H*-1,2,4-triazole-5-one) titrated with 0.05 M TBAH in isopropyl alcohol, *t*-butyl alcohol, acetonitrile and N,N-dimethyl formamide at 25 °C

TABLE-1
HALF-NEUTRALIZATION POTENTIAL (HNP) VALUES AND THE CORRESPONDING pKa VALUES OF ALL TRIAZOLE DERIVATIVES IN ISOPROPYL ALCOHOL, *tert*-BUTYL ALCOHOL, ACETONITRILE AND DMF

Compd. No.	Isopropyl alcohol		*tert*-Butyl alcohol		N,N-Dimethyl formamide		Acetonitrile	
	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)
2a	13.02	-303.8	14.19	-378.9	14.51	-392.4	13.75	-342.3
2b	12.82	-298.9	14.20	-374.5	14.50	-398.7	14.32	-379.2
2c	12.13	-248.0	14.35	-383.3	14.30	-378.7	13.24	-315.2
2d	12.40	-280.1	14.35	-383.8	14.48	-394.9	13.77	-357.5
2e	12.74	-286.3	14.41	-385.2	14.97	-422.5	14.24	-376.1
2f	10.93	-185.3	11.59	-220.7	13.42	-328.4	12.06	-243.2
3a	12.63	-277.5	13.66	-340.9	13.29	-317.3	13.34	-325.3
3b	12.77	-287.5	13.72	-351.7	13.39	-327.5	13.84	-349.1
3c	12.67	-294.7	13.76	-356.9	13.89	-353.3	13.31	-332.0
3d	12.78	-285.9	13.46	-326.4	13.85	-354.1	13.70	-325.1
3e	13.73	-341.2	14.63	-395.1	15.43	-444.0	15.10	-423.0
3f	13.09	-304.8	12.89	-292.3	13.12	-304.8	14.07	-362.2

The pH of the weak acids are given by the following equation:

$$pH = pKa + \log [A^-]/[HA]$$

pH = pKa occurs when $[A^-]$ is equal to [HA] at the half-neutralization point. Therefore, the pH values can be regarded as pKa at the half-neutralization points. When

the dielectric permittivity of solvents is taken into consideration, the acidic arrangement can be expected as follows: N,N-dimethyl formamide (ε = 36.7) > acetonitrile (ε = 36) > isopropyl alcohol (ε = 19.4) > *t*-butyl alcohol (ε = 12). The pKa values of all triazole derivatives in these solvents are given Fig. 7. In isopropyl alcohol, all these compounds show the strongest acidic properties.

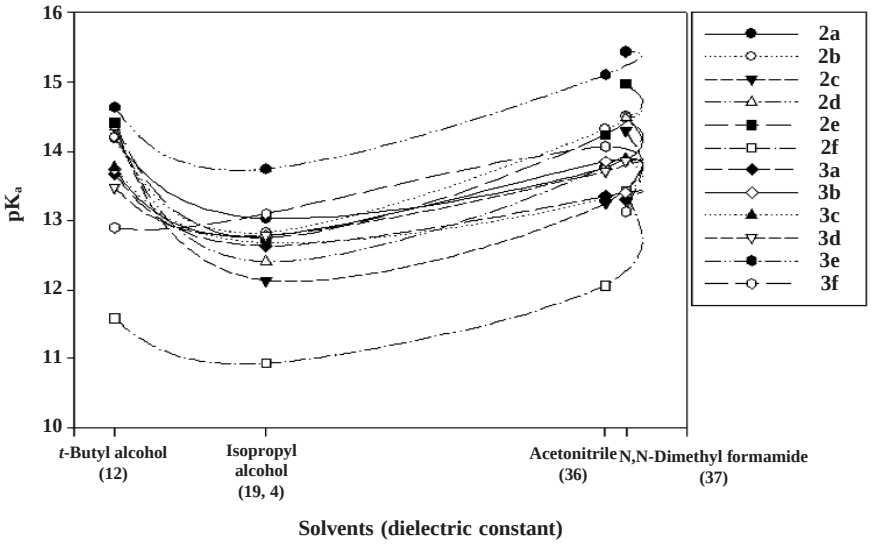


Fig. 7. Exchange of the pKa values with dielectric constant

The degree to which a pure solvent ionizes was represented by its autoprotolysis constant, K_{SH}. For the above reaction the constant is defined by

$$K_{SH} = [H_2S^+]\cdot[S^-]$$

Autoprotolysis is an acid-base reaction between identical solvent molecules in which some act as an acid and others as a base. Consequently, the extent of an autoprotolysis reaction depends both on the intrinsic acidity and the instrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. The exchange of the pKa values with autoprotolysis constant are given in Fig. 8.

The acidity of a compound depends on several factors. The two most important factors are the solvent effect and molecular structure. Table-1 shows that the half-neutralization potential (HNP) values and the corresponding pKa values obtained from potentiometric titrations depend on the type of non-aqueous solvents used and molecular structure of the compound.

As seen in Table, the acidic order for compounds **2a**, **2d**, **2e** and **3c** is: isopropyl alcohol > acetonitrile > *t*-butyl alcohol > N,N-dimethyl formamide, for compounds **2b**, **2f**, **3d** and **3e** is: isopropyl alcohol > *t*-butyl alcohol > acetonitrile > N,N-dimethyl formamide, for compound **2c** is: isopropyl alcohol > acetonitrile > N,N-dimethyl formamide > *t*-butyl alcohol, for compound **3a** is: isopropyl alcohol > N,N-dimethyl

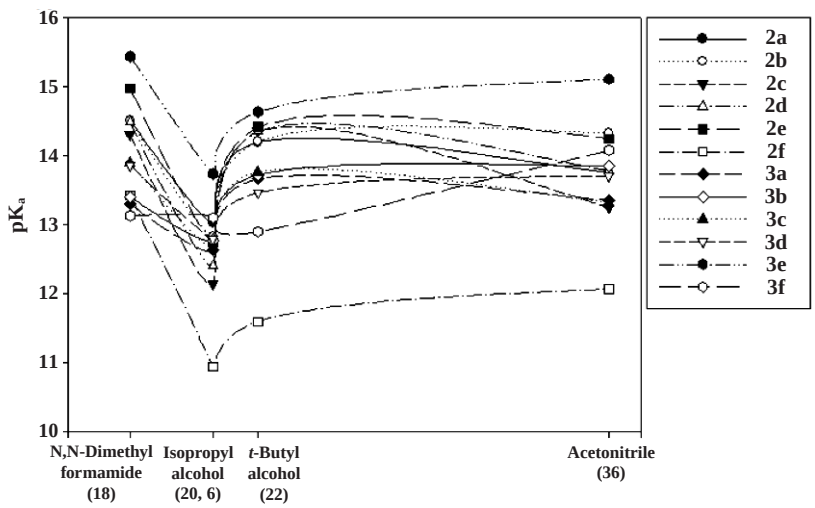


Fig. 8. Exchange of the pKa values with autoprotolysis constant

formamide > acetonitrile > *t*-butyl alcohol, for compound **3b** is: isopropyl alcohol > N,N-dimethylformamide > *t*-butyl alcohol > acetonitrile, for compound **3f** is *t*-butyl alcohol, isopropyl alcohol > N,N-dimethyl formamide > acetonitrile. In isopropyl alcohol, **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **3a**, **3b**, **3c**, **3d** and **3e** compounds show the strongest acidic properties, in *t*-butyl alcohol, **3f** compound shows the strongest acidic properties. **2a**, **2b**, **2d**, **2e**, **2f**, **3c**, **3d** and **3e** compounds show the weakest acidic properties in N,N-dimethyl formamide, **2c** and **3a** compounds show the weakest acidic properties in *t*-butyl alcohol, **3b** and **3f** compounds show the weakest acidic properties in acetonitrile. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in the amphiprotic neutral solvents. Autoprotolysis is an acid-base reaction between identical solvent molecules is which some act as an acid and others as a base.

Consequently, the extent of an autoprotolysis reaction depends both on the intrinsic acidity and the instrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. The acidity of a compound depends on mainly two factors, *i.e.* solvent effect and molecular structure. Half-neutralization potential (HNP) values and corresponding pKa values obtained from the potentiometric titrations rely on the non-aqueous solvents used and the substituents at C-3, in triazole ring.

REFERENCES

1. A. Loupy, Microwaves in Organic Synthesis, Wiley-VCH, Weinheim (2002).
2. R.S. Varma and R. Dahiya, *Tetrahedron Lett.*, **39**, 1307 (1998).
3. A. Lengar and C.O. Kappe, *Org. Lett.*, **6**, 771 (2004).
4. Y. Xu and Q.X. Guo, *Heterocycles*, **63**, 903 (2004).
5. B. Kahveci, M. Özil and M. Serdar, *Heteroatom Chem.*, **19**, 38 (2008).
6. L. Botella and C. Najera, *Tetrahedron Lett.*, **45**, 1833 (2004).

7. J.A. Farand, I. Denissova and L. Barriault, *Heterocycles*, **62**, 735 (2004).
8. D. Ferguson, *Mol. Div.*, **6**, 281 (2003).
9. G. Kortüm, W. Vogel and K. Andrussow, Dissociation Constants of Organic Acids in Aqueous Solution, Plenum Press, New York (1961).
10. V.A. Palm, Tables of Rate and Equilibrium Constants of Heterolytic Organic Reactions, Viniti, Moscow (1976).
11. K. Izutsu, Acid-base Dissociation Constants in Dipolar Aprotic Solvents, IUPAC Chemical Data Series No. 35, Blackwells Scientific, Oxford (1990).
12. F.G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).
13. H.H. Takimoto, G.C. Denault and S. Hotta, *J. Heterocycl. Chem.*, **3**, 119 (1966).
14. R. Milcent and C. Redeuilh, *J. Heterocycl. Chem.*, **16**, 403 (1979).
15. R. Milcent and P. Vicart, *J. Med. Chem.*, **18**, 215 (1983).
16. A.R. Katritzky and K.S. Laurenzo, *J. Org. Chem.*, **53**, 3978 (1988).
17. A.A. Ikizler, A. Ikizler and N. Yildirim, *Monatsh. Chem.*, **122**, 557 (1991).
18. A.A. Ikizler and H. Yüksek, *Collect. Czech. Chem. Commun.*, **59**, 731 (1994).
19. B. Kahveci and A.A. Ikizler, *Turk. J. Chem.*, **24**, 343 (2000).
20. B. Dash, M. Patra and P.K. Mahapatra, *J. Indian Chem. Soc.*, **60**, 772 (1983).
21. H. Emilsson, H. Selander and J. Gaarder, *Eur. J. Med. Chem.-Chim. Ther.*, **20**, 333 (1985).
22. B. Kahveci, O. Bekircan, M. Serdar and A.A. Ikizler, *Indian J. Chem.*, **42B**, 1527 (2003).
23. B. Kahveci, O. Bekircan and S.A. Karaoglu, *Indian J. Chem.*, **44B**, 2614 (2005).
24. S.H. Herbert and C.M. Birdsall, *J. Am. Chem. Soc.*, **65**, 54 (1943).
25. B. Nowak and Z. Pawlak, *J. Chem. Soc., Faraday Trans. I*, **78**, 2693 (1982).
26. G. Wada, E. Tamura, M. Okina and M. Nakamura, *Bull. Chem. Soc. (Japan)*, **55**, 3064 (1982).
27. F. Köseoglu, E. Kiliç and A. Dogan, *Anal. Biochem.*, **277**, 243 (2000).
28. D.L. Hughes, J.J. Bergan and E.J.J. Grabowski, *J. Org. Chem.*, **51**, 2579 (1986).
29. E.R. Benesch and R. Benesch, *J. Am. Chem. Soc.*, **77**, 5877 (1955).
30. J.T. Edsall and M.H. Blanchard, *J. Am. Chem. Soc.*, **55**, 2337 (1933).
31. O. Bekircan, B. Kahveci and O.B. Ozgumus, *Chin J. Chem.*, **25**, 1871 (2007).
32. Z.A. Kaplancikli, G. Turan-Zitouni, A. Ozdemir and G. Revial, *Eur. J. Med. Chem.*, **43**, 155 (2008).
33. O. Bekircan, B. Kahveci and M. Kucuk, *Turk. J. Chem.*, **30**, 29 (2006).
34. H. Emilsson, K. Luthman and H. Selander, *Eur. J. Med. Chem.*, **2**, 235 (1986).
35. G. Turan-Zitouni, Z.A. Kaplancikli and A. Ozdemir, *IL Farmaco*, **57**, 573 (2002).
36. N. Demirbas, S.A. Karaoglu, A. Demirbas and K. Sancak, *Eur. J. Med. Chem.*, **39**, 793 (2004).
37. H. Yüksek, Z. Ocak, M. Ozdemir, M. Ocak, M. Bekar and M. Aksoy, *Indian J. Heterocycl. Chem.*, **13**, 49 (2003).
38. H. Yüksek, O. Üçüncü, M. Alkan, Z. Ocak, S. Bahçeci and M. Özdemir, *Molecules*, **10**, 961 (2005).
39. H. Yüksek, S. Bahçeci, Z. Ocak, M. Özdemir, M. Ocak, B. Ermis and T. Mutlu, *Asian J. Chem.*, **17**, 195 (2005).
40. H. Yüksek, S. Bahçeci, Z. Ocak, M. Alkan, B. Ermis, T. Mutlu, M. Ocak and M. Özdemir, *Indian J. Heterocycl. Chem.*, **13**, 369 (2004).
41. A.A. Ikizler and R. Ün, *Chim Acta Turc.*, **7**, 269 (1979).
42. B. Kahveci and A.A. Ikizler, *Acta Poloniae-Pharmaceutica-Drug Res.*, **57**, 119 (2000).
43. N. Demirbas, R. Ugurluoglu and A. Demirbas, *Bioorg. Med. Chem.*, **10**, 3717 (2002).

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